TUMOUR VOLUME AND OCCURANCE OF PULMONARY METASTASIS IN LIPOSARCOMA OF THE EXTREMITIES

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2.1 ABSTRAK

Liposarkoma atau barah tisu lemak merupakan salah satu barah yang paling kerap dihidapi di kalangan barah tisu lembut, biasanya meliputi 9.8 ke 18%. Badan Kesihatan Sedunia (WHO) telah membahagikan liposarkoma kepada beberapa bahagian mengikut jenis tisu seperti “well differentiated”, “myxoid”, “pleomorphic” dan “dedifferentiated”. Barah tisu lembut didapati kerap merebak ke paru paru, dan kebarangkalian kekerapan merebak ini bergantung kepada jenis sub- barah liposarkoma ini.

Penyakit barah tisu yang telah merebak merupakan antara penyebab kematian yang paling utama. Oleh itu pengesanan awal barah yang merebak amatlah penting kerana ia memberi kesan kepada rawatan serta prognosis pesakit. Saiz barah sebelum ini telah dikenalpasti sebagai antara risiko yg penting namun kekurangan data dalam menyokong faktor ini disebabkan oleh data yang tidak lengkap serta tepat. Namun, kini telah terdapat pelbagai kaedah untuk mengukur saiz barah dengan lebih tepat iaitu dengan teknik pengiraan melalui program OsiriX. Di mana program ini mengukur isipadu barah melalui imej CT atau MRI yang telah dimuat turun ke program ini. Setelah itu analisa data dilakukan bagi mendapatkan kaitan antara isipadu barah dengan “survival” keseluruhan liposarkoma. Selain itu, faktor lain yang boleh memberi kesan terhadap barah ini turut dikenalpasti seperti data demografik, diagnosis tisu, kawasan pembedahan dan implikasi barah seperti barah merebak ke paru paru, kes berulang serta kematian turut disiasat serta dianalisis.

Kajian ini melibatkan sejumlah 38 pesakit yang memenuhi kriteria yang diperlukan, dan telah dipilih dari 1 January 2001 hingga 31 Disember 2014.

Daripada hasil kajian yang telah dilakukan, terdapat perbezaan antara isipadu barah dengan jenis liposarkoma, di mana barah yang lebih agresif mempunyai isipadu barah yang lebih kecil. Selain itu, isipadu barah yang besar turut berkait dengan kedalaman diameter barah,ketiadaan rawatan kemoterapi serta barah paru paru yang merebak. “Survival” keseluruhan liposarkoma dalam kajian ini turut dipengaruhi oleh barah paru paru yang merebak. Turut didapati dalam kajian ini, isipadu barah serta faktor lain tidak mempengaruhi “survival’ pesakit.

Dengan ini kesimpulan yang dapat diolah daripada kajian ini ialah terdapat kaitan yang penting antara isipadu barah dengan kedalaman barah sendiri, ketiadaan rawatan kemoterapi serta barah paru paru yang merebak. Survival keseluruhan pesakit di dalam kajian ini hanya dipengaruhi oleh barah yang merebak ke paru paru, dan tidak dipengaruhi oleh isipadu barah.

2.2 ABSTRACT

Liposarcoma is one of the commonest subtypes of soft tissue sarcoma constituting 9.8-18 % of cases [1]. The World Health Organization (WHO) classification of tumors of soft tissue and bone 2009 clasiffied liposarcoma into 4 subtypes which were well differentiated, myxoid, pleomorphic and dedifferentiated subtypes. Soft tissue sarcomas metastasize primarily via hematogenous spread in which they usually settled in pulmonary as the main site. Liposarcoma metastasized according to the grade of lesion where high grade liposarcoma had the highest metastasis rate which was 50 % (3).

Metastatic disease is the major cause of death in patients with soft tissue malignancies. Hence early detection of metastatic disease has important implications for prognosis and treatment. Tumor size was a readily available risk factor but it has been neglected in large analyses of prognostic factors largely because of its incompleteness and inaccuracy. Tumor volume measurement recently was found to be as accurate and reproducible to be used as prognostic indicator.

Therefore we decided to measure the tumor volume via 3- dimensional views from CT or MRI and used OsiriX program to interprete the tumor volume. Then we established the association of tumor volume with overall survival in liposarcoma. Other than that, we also associate other prognostic factors such as demography, histopathological diagnosis, surgical margins and the disease outcome for instance pulmonary metastasis, local recurrence and death with the surgically treated liposarcoma and its overall survival.

This study involved a total of 38 patients which fulfilled the inclusion and exclusion criteria, were selected from 1st January 2001 till 31st December 2014.

We found out there were differences with median tumor volume according to liposarcoma subtypes, with higher grade tumor presented with smaller tumor volume. Larger than median tumor volume was associated in patients with increased depth of tumor, absence of adjuvant chemotherapy and presence of pulmonary metastasis. Overall survival in our study was significantly influenced by presence of pulmonary metastasis. Tumor volume and other prognostic factors were not associated with worsening overall survival.

Therefore we made the conclusion there was significant association between tumor volume with increased depth of tumor, absence of adjuvant chemotherapy and presence of pulmonary metastasis. Overall survival in this study was associated with presence of pulmonary metastasis and was not influenced by the tumor volume.

3.0: INTRODUCTION

Liposarcoma is one of the commonest subtypes of soft tissue sarcoma constituting 9.8-18 % of cases [1]. The incidence peaks between 40-60 years and there is slight male predominance [2]. The World Health Organization Classification of tumors of soft tissue and bone 2009 clasiffied liposarcoma into 4 subtypes: well differentiated liposarcoma/ atypical lipomatous tumor, myxoid liposarcoma, pleomorphic liposarcoma and dedifferentiated liposarcoma.[24,12]

Liposarcoma commonly metastasize to the lung via hematogenous spread. Metastasis disease is the major cause of death and understanding prognostic factors is important for early detection and treatment of metastasis disease has important implications for prognosis and treatment. Myxoid, pleomorphic and dedifferentiated liposarcoma had been reported to have higher incidence of early pulmonary metastases and local recurrence. However other factors such as size, depth of tumor, sites and also implicated to final survival of patients. Roger at al stated that survival rates is the highest for extremity liposarcoma (93%; 53 months overall survival rate) with 11% were contributed by high grade liposarcoma.[59] This is further supported by Robert MC et al in which 2 years and 5 years survival rate for well differentiated liposarcoma was 92% and 84% respectively, while for pleomorphic liposarcoma which is high grade reported poor survival rate of 70% in 2 years and 50% in 5 years. The size of tumor does strongly contribute to patient's prognosis. As stated by Kilpatrik et al evaluating prognostic factors in his study of 95 cases with myxoid and round cell liposarcoma between 1971 and 1992 showed that the tumor size has an independent prognostic impact.[45] A few other studies done by Reitan JB et al and Orson GS et al reported

that larger tumor size is associated with poor survival rate in liposarcoma patients.[68,63] However, all the studies done were using single dimension to determine the tumor size.

Liposarcoma usually presented with painless asymptomatic growing mass. Most of our patient presented late with huge size of tumor before had surgical treatment. Tumor size is one of the negative prognostic factors for liposarcoma survival. However, in large tumor the objectivity measurement of size was not definite and accurate. A tumor volume measurement method is an accurate and reproducible and more objective in assessments the size and used as prognostic indicator. There is numerous ways on how tumor volume was calculated in previous studies. Beiling et al. 1996 calculated absolute tumor volume by using ellipsoid formula from the three parameters of length, width and depth of the tumor determined from two plane X-rays films.[5] Meanwhile, Shin et al 2000 measured the tumor volume by ellipsoid mass formula not only on plain radiography but also on MRI film. Furthermore, he also measured the total tumor volume with three dimensional MRI.[71] Until now, despite being the commonest soft tissue sarcoma, there has not been any study conducted to find association between tumor volume and the occurrence of pulmonary metastasis in liposarcoma.

Therefore this study is designed with an objective to look for any association between the tumor volume and pulmonary metastasis of liposarcoma especially for high volume tumor due to late presentation.

4.0: LITERATURE REVIEW

4.1 EPIDEMIOLOGY

Sarcoma is a heterogeneous group of mesenchymal malignancy. It is rare malignancy which accounts for 1% of adult tumor and 15% of pediatrics age group tumor [24]. Approximately 80% of sarcoma arises from soft tissue and 20 % from bone[83]. In the United States, around 8700 new soft tissue sarcoma were diagnosed yearly and 1500 cases annually in the UK [9]. On the other hand, in Asia pacific region, 18000 new cases of sarcoma of bone and soft tissue were reported which accounts around 14400 soft tissue sarcoma cases expected each year[83]. There were more than 50 histological subtypes of STS were identified with each having unique clinical, prognostic and therapeutic features (WHO). Therefore a multidisciplinary approach is mandatory to minimize recurrence, maximize survival and preserve functionality and quality of life [48].

Liposarcoma is the second commonest STS after Pleomorphic sarcoma which contributes around 20 to 30% of all adult sarcoma[24,7,53]. It is divided in 5 subtypes, with well differentiated being the commonest with 40 - 45 % of all tumors[24,12]. Like all other malignancies, liposarcoma become more prominent with increasing age with median age of 56-58 years old[42,28]. There is slight male predominance[28,52]. It is commonly found in the lower extremities, as pelvis and thigh region being the predominant sites. These findings were supported with what has been reported worldwide[53,24,59]. In most literature, the retroperitoneum and lower extremities were reported to have high incidence of large tumors.

4.2. SUBTYPES OF LIPOSARCOMA

4.2.1 Classification

Liposarcoma can be categorized in 3 biological grade based on molecular and cytogenic studies which contain 5 different subtypes based on WHO[24,12]. The low grades which include well differentiated subtypes, followed by intermediate grade encompassing of myxoid and round cell subtypes. The myxoid type is further classified in 3 groups based on the round cell composition. And last but not least are the high grade types which are pleomorphic and dedifferentiated liposarcoma.

4.2.2 Age and site of involvement

The common site for liposarcoma is lower extremities with high incidence in thigh followed by retroperitoneum [63]. Based on WHO, well defferentiated liposarcoma commonly occur in deep soft tissue of limbs especially in thigh. It affects the middle aged group with peak incidence in 6th decade of life. [24,12]. As for dedifferentiated liposarcoma, it shares the same population aged as WD liposarcoma as dedifferentiation occurs in 10% of WD liposarcoma of any subtypes. It tends to occurs in retroperitoneum compare to extremities with the ratio of 3:1. Furthermore, myxoid liposarcoma usually occurs in deep soft tissue of extremities with more than two third from thigh musculature. It is a disease of young adults with peak incidence between 4th to 5th decade. Although it is very rare, it is the commonest form of liposarcoma in patient younger than 20 years old. Pleomorphic sarcoma commonly found in extremities, particularly the thigh (lower > upper) and rarely affects retroperitoneum and trunk, with common occurrence in aged more than 50 years old. [30]. True mixed liposarcoma

is extremely rare and predominance in elderly. Most cases are found in intraabdominal and retroperitoneum.

4.2.3 Gender

There is no gender predilection in al subtypes of liposarcoma.

4.2.4 Tumor size

Due to painless and slow growing nature of the tumor, liposarcoma can grow into enormous size before being diagnosed. The largest size reported in few studies can reach up to 45cm at presentation not specific to any subtypes or liposarcoma [63, 45]. In a study involving myxoid and round cell liposarcoma, the cutoff point of tumor is more than 10cm (in greatest dimension) is associated with high incidence of metastasis with poor prognosis. The significant good prognostic indicator as mentioned by Orson GG in 1987 is tumor size less than 15cm, histological grade (WD liposarcoma and low grade myxoid liposarcoma has a better prognosis), and surgical stage (no distance metastasis has a good outcome) [63]. Reitan et al, 1985 concludes that better survival is found in small tumor and this was supported by other studies worldwide [68]. The progression of disease apparently correlates with the size of tumor but Gustafson et al, 1985 and Rezsel et al founds no significant correlation between size and tendency to metastasis [28, 69]. They are not much study available which correlate individual subtypes of liposarcoma size with occurrence of metastasis.

4.2.5 Histopathology of subtypes

4.2.5.1 WELL DIFFERENTIATED (WD) LIPOSARCOMA/ ATYPICAL LIPOMATOUS TUMOR (ALT)

ALT/WD liposarcoma is locally aggressive mesenchymal neoplasm. It represents the most common subtypes (40-45% reported). Macroscopically, it varies from yellow to white-grey with soft, rubbery firm consistency. Histologically, it can be subdivided into 4 types; adipocytic, spindle cells, inflammatory and spindle. Generally, WD liposarcoma compose of either entirely or partly mature adipocytic proliferation with cell size variation and focal nuclear atypia in both adipocytes and stromal cells. In addition to that, the presence of scattered stromal cells which is hyperchromatic and often multinucleated with lipoblasts which are monovacuolated or multivacuolated lipoblasts may contribute to diagnosis. There is no gender preference.

4.2.5.2 DEDIFFERENTIATED LIPOSARCOMA (DDL)

DDL is a malignant adipocytic neoplasm showing transition from ALT/WD liposarcoma to non lipogenic sarcoma of variable histological grade either in primary (around 90%) or recurrence (10%) group. The transition occurs in up to 10% of WD liposarcoma and the risk increases in deep seated lesion. DDL most probably represents a time dependent rather than site dependent. Grossly, it appear as large multi nodular yellow masses with solid often tan grey non lipomatous (dedifferentiated) area which often show necrosis. Histological hallmark is an abrupt transition from WDLPS to non lipogenic sarcoma which usually is high grade. There are varieties of histological appearance in dedifferentiation areas. Generally it is

divided into undifferentiated pleomorphic sarcoma or intermediate to high grade myxofibrosarcoma and low grade dedifferentiation.

4.2.5.3 MYXOID LIPOSARCOMA

ML composed of delicate plexiform capillary network associated with variable numbers of lipoblast and primitive mesenchymal like cells with diffuse myxoid stroma. Grossly it appears soft, pink tan with mucinous surface. The morphological variant in term of identical chromosomes abnormalities of myxoid liposarcoma is round cell liposarcoma. Round cell shows histological progression to hypercellular or round cell morphology which associated with poorer prognosis. It is manifest as presence of sheets of round blue cells with clear to eosinophilic cytoplasm. Strong evidence myxoid and RC liposarcoma represents histological continuum of MLS is the present of gradual transition from myxoid to hypercellular/ RC areas commonly observed in MLS.

4.2.5.4 PLEOMORPHIC LIPOSARCOMA

PL is a pleomorphic, high grade sarcoma containing variable number of pleomorphic lipoblasts with abnormal mitotic figure and area of hemorrhage and necrosis. Macroscopically, it presents in pink-tan to brown lesion suggestive of area of hemorrhage and necrosis. No areas of ALT or another line of differentiation are evident. Histologically, infiltrative margins are present in most cases and varying proportion of pleomorphic lipoblasts can be found in all tumors with background of high grade usually pleomorphic sarcoma. Focal areas of similar to intermediate to high grade myxofibrosarcoma with pleomorphic lipoblasts can be seen in almost half of cases.PL is the rarest subtype of

liposarcoma, contributes to 5% of all liposarcomas and 20 % of pleomorphic sarcomas. This subtype has a strong predilection to deep soft tissues of proximal extremities especially thigh accounts for 30-40% of cases [30]. In the latest study by Mentzel et al and Downes et al combined, reported that the vast majority of cases (80%) are deep seated/ or extra compartmental with 20% cases were superficial [56,14]. Local recurrence and metastasis rates are 30-50% with overall survival of about 60%. Common site of metastasis is the lung.

4.2.5.5 MIXED LIPOSARCOMA

It is combination of all the subtypes mentioned. Mixed liposarcoma is the rarest types of tumor which affects the elder population. Grossly, most cases are large and often multinodular with cystic and solid area and grey-yellow cut surface. Microscopically, it is visualized as mixed of subtypes of liposarcoma such as present of myxoid area in the WDLPS/DDLPS or rare mixed type show combination of myxoid and round cell.

Generally, staging for tumor can be divided into two categories, local and distant staging. Local staging comprises of plain X-ray, Computed Tomography (CT) scan and Magnetic Resonance Imaging (MRI). On the other hand, distant staging consists of CT scan and radio-isotope scan depending on part which is commonly involves. Soft tissue sarcoma per se spread hematogenously, in particularly the lung. Hence CT scan is mandatory to perform provided chest x- ray shows significant abnormalities.

4.3 LOCAL STAGING

3.1.1 Plain film Radiography

Plain x- ray has a little role in diagnosing soft tissue tumor as compared to primary bone tumor. The well recognized limitation of plain x- ray is lack of contrast resolution. However, the limitation should not be underestimated as it can still provide valuable information such as detecting matrix calcification, periosteal reaction and cortical destruction in soft tissue tumors. Plus it is an easy, cheap and universally available tool [13].

3.1.2 CT Scan as local staging.

CT scan has a little value in diagnosing primary soft tissue tumors as compared to bone tumors.

3.1.3 MRI as local staging

MR has become the preferred modalities for primary soft tissue tumor evaluation as it provides superior soft tissue contrast resolution. Besides, it have provides true multiplanar images in axial, sagittal and coronal and devoid of artifacts which commonly appears in CT scan[81, 87]. Plus it has the ability to produce accurate diagnosis by delineating the soft tissue extent of the tumor. [75]

The intensity of signal varies from low (black) to high (white), depending on chemical composition of the soft tissues and the modalities of execution. T1 and T2 weighted image

has a different signal intensity depending on the used times. Intravenous administration of gadolinum enhances hypervacular lesion and results in high signal intensity in T1 weighted images. STIR (Short T1 inversion recovery) supresses fat signal so gadolinum enhanced signal intensity are contrasted against black bone marrow or soft tissue fat.

The subtypes of liposarcoma manifest differently in MR images. Few studies have been done to evaluate the different subtypes of liposarcoma in MRI. WD liposarcoma has the appearance of high SI (signal intensity) lesion on T1 weighted image corresponding to fat with fine septae within it, intermediate SI mass iso-intense with adjacent subcutaneous fat in T2 weighted images and faint enhancement of lesion post gadolinum suggestive of little vascularity. As for myxoid liposarcoma, T1 weighted image shows homogenous mass isointense with muscle and homogenous high SI with linear septae in T2 weighted images. Post contrast usually shows heterogenous non-enhancing areas which corresponds with accumulated mucinous material with no capillary network. Pleomorphic and dedifferentiated liposarcoma are aggressive and high grade sarcomas. Haemorrhage and necrosis are usually present with high degree of cellular pleomorphism. On T1 and T2 weighted image shows heterogenous mass containing low and high SI, indicates area of haemorrhage and necrosis with marked heterogenous enhancement post gadolinum which shows rich vascularity of this lesion [3,15,11].

In conclusion, MR images play the central role in diagnosis soft tissue tumor. However, the baseline imaging should still start with plain radiography and proceed with other imaging algorithms if needed. Biopsy is mandatory if malignancy is suspected as histology still remains the gold standard for diagnosis [13].

3.1.4 Comparing CT and MRI as local staging

It has been well established that the MR imaging is more superior to CT scan. This is because MRI able to depict tumor boundaries and delineate interface between tumor and surrounding soft tissue, generally fat and muscle.[4] It also can demonstrate the anatomical relationship with neurovascular structures better as compared to CT. Besides, the extent of bone marrow abnormality can be visualized clearly. [2]

Furthermore, the advantage of multiplanar images (coronal, saggital and axial) from MRI adds on the superiority in visualizing the tumor from CT scan. CT is superior to MRI in showing mineralized tissue such as bone and calcium deposition [13]. Sundaram M and colleagues, 1990 concludes that even though the rim of sclerotic bone not seen in MRI can be pictured well in CT but it adds to no additional information to what that already available in plain x- rays. [73]

Panicek et al in 1999 concludes that CT and MR imaging are equally accurate in local staging of primary soft tissue and bone tumors.[88]

In general, MR is superior to CT in studying the soft tissues, bone marrow and spine, while CT scan in better to study calcified tissues as well as the best imaging modalities for pulmonary metastasis.

3.2 Distant staging

Soft tissue sarcoma spread via hematogenous, particularly in lung. Nicholas et al, 2005 reported that pleomorphic and dedifferentiated liposarcoma (high grade) has a high tendency to metastasize to lungs as compared to myxoid subtype which favors extra pulmonary metastasis.[51] Michelle AG et al, stated high number of pulmonary metastasis in high grade subtypes with tumor size more than 5cm but statistically not significant.[27] CT is the best modalities to detect pulmonary nodules. It has the accuracy of 99.6% in detecting pulmonary spread and its sensitivity is greater than plain radiography and traditional tomography. Therefore, CT should be done as initial evaluation for patient suspected to have primary soft tissue malignancy. However, not to forget chest x- ray as a screening tool for lung metastasis with the accuracy of 96.6%.[7] Extended roles of CT scan apart from distal staging include surveillance of pulmonary metastasis and restaging for pulmonary metastasis after chemotherapy.

4.4 TUMOUR VOLUME CALCULATION USING OSIRIX

As we know, tumor size is an important and easily obtainable prognostic factor and may serve as a risk stratified therapy. Most studies that evaluate size as risk factors only take consideration of the largest diameter which traditional measured in one single dimension of the primary tumor. However, the best method to determine tumor size is yet to be established. Tumor size measurement method should be accurate and reproducible because it is going to be used as prognostic factors. There were few studies done previously to evaluate method to be used in measurement of size.

Tumor volume has been measured using ellipsoid mass formula using plain radiograph and MRI or clinically by largest diameter of resected specimens or direct three dimension in MRI or CT scan. Somville J et al 2001, studied on reliability of measuring tumor volume by different methods for tumors of musculoskeletal systems. He stated that although tumor size which is expressed by maximal diameter is an easy and readily available data, but the measurement itself shows an error of 5% which relatively considered a large error for a simple measurement. Plus, it is difficult to determine the largest diameter in irregular borders. He concludes that size is not equivalent to volume and is not reliable as a parameter for volume. [72]

Study by Beiling P et al 1996 of tumour volume and prognosis in osteosarcoma used tumour dimension from plain xrays. He obtained tumor size by using absolute tumor volume (ATV) calculated from three parameters of length, depth and width by ellipsoid formula (0.52 x ATW X ATL X ATD). The cut off point for ATV of > 150cm3 is associated with high risk of pulmonary metastasis.[5]

The limitation of plain radiography and CT scan is the tendency to underestimate tumor size due to inadequacy of soft tissue visualization and poor differentiation between adjacent soft tissue and tumor. Hence, MRI is the best modality for defining tumor margin by delineating soft tissue components.

Furthermore, measuring tumor volume in soft tissue sarcoma is somewhat different from measuring volume of other tissue such as liver, kidney or other organ.[23,64,19] Due to the nature of tumor with irregular borders, making ellipsoidal method unfit, thus volume maybe measured using three dimensional method accurately.

Hence, Shin KH et al 2000, reported on the best methods to calculate tumor volume using the similar ellipsoidal method as Beiling et al which he applied on radiograph, CT scan and MRI.[71,5] He studied three methods of evaluating tumor volume by using volume measurement with ellipsoid mass formula by radiograph and MRI and three dimensional volume measurement in MRI. He concludes that measurement of tumor volume by three dimensional in MRI is more reproducible with sensitivity of 89% and specificity of 73%.

OsiriX is an open source, FDA approved, Digital Imaging Communication Medicine (DICOM) software invented by Rosset et al from University of Geneva (2003-2009).[7o] It is a highly functional program that allow user to reconstruct and manipulate 3D images and coordinate data. The most important preoperative evaluation and surgical planning for disease pathology is volume rendering and multiplanar reformatting (MPR).[33] Hence, this program is flexible in terms of it does not only cater for radiologist, but clinician too have an easy readily access to reconstruct 3D images for further surgical planning.[33,52,80]

The OsiriX software program was developed as an application for MacOS X. This program works by updating the images automatically, followed by processing and manipulation into multidimensional image navigation and visualization. [13,26] This program was able to convert both 2D and 3D images acquired either from CT or MRI, or even from PET/CT scanners as well. The images can be obtained from PACS using a DICOM store function. It can also be "pulled" from DICOM query- retrieve function of the program.

The accuracy and reliability of OsiriX has been approved by other studies done worldwide. For instance, a very precise 3D analysis of cervical spinal canal by reconstructing data from MD-CT cervical spine using OsiriX has reported its potential benefits which is equivalent values to commercial software and provides reliable 3D information (Tomonari Y et al 2009).[77,80,84] Furthermore, G Kim et al,2012 demonstrated less than 0.3mm accuracy and high reliability by using OsiriX in his study on kinematics analysis of the knee.[41] This is further supported by Fortin M et al, 2012 in his study of paraspinal measurement concludes that OsiriX yielded measurements with high intra- rater and inter-software reliability.[25] In a nutshell, OsiriX is a trustable and accurate software which can be use readily for medical imaging.

4.5 STAGING

Staging is a process of interpreting clinical, imaging and histopathologic results in order to establish clinical diagnosis and to access the extent of cancer spread. It also aid to determine the prognosis and guide treatment options. There are two commonly used staging for musculoskeletal tumor which are Enneking Classification and TNM Staging of American Joint Committee on Cancer (AJCC) system.[20,83,85]

Table 1: The TNM staging of AJCC system is frequently used for soft tissue sarcoma staging.

Stage	*Grade*[a]	*Primary tumor*[b]	*Metastasis in regional lymph nodes*[c]	*Distant metastasis*[d]
IA	G_1 or G_2	T_1	N_0	M_0
IB	G_1 or G_2	T_2	N_0	M_0
IIA	G_3 or G_4	T_1	N_0	M_0
IIB	G_3 or G_4	T_2	N_0	M_0
III	Not defined			
IVA	Any G	Any T	N_1	M_0
IVB	Any G	Any T	Any N	M_1

[a]G_1 = Well differentiated; G_2 = moderately differentiated; G_3 = poorly differentiated; G_4 = undifferentiated. Ewing's sarcoma and malignant lymphoma are graded as G_4.
[b]T_1 = Tumor confined within the cortex; T_2 = tumor extends beyond the cortex.
[c]N_0 = No metastasis in regional lymph nodes; N_1 = metastasis in regional lymph nodes.
[d]M_0 = No distant metastasis; M_1 = distant metastasis.